REMARKS

Following entry of this amendment, claims 1-5, 7, 9-19, and 21-25 are pending in the application. Claims 6, 8, and 20 have been cancelled without prejudice or disclaimer. Support for the amendments to claim 1 can be found in the specification, e.g., at page 8, second paragraph, and at page 8, third paragraph. Support for the amendments to claims 2-5, 7, 9, 13-16, and 24 can be found in the specification, e.g., at page 8, second paragraph. Claim 25 has been amended to reflect more conventional method claim language.

Specification

The Examiner objected to the Abstract because it contains more than one paragraph. Action at page 2. Applicants submit a substitute page 25 with an Abstract that is only one paragraph and request that page 25 of the specification be replaced with the substitute page 25. Substitute page 25 merely combines the two paragraphs from original page 25 and thus adds no new matter.

Rejection under 35 U.S.C. §§ 112 and 101

The Examiner rejected claim 25 under 35 U.S.C. § 112, first paragraph, alleging that the claim is indefinite because it "does not set forth any steps involved in the method/process, [so] it is unclear what method/process applicant is intending to encompass." *Id.* The Examiner also rejected claim 25 under 35 U.S.C. § 101, alleging that it is "not a proper process claim." *Id.* Solely to expedite prosecution and without acquiescing to the rejection, Applicants have amended claim 25 to reflect more conventional method claim language. In view of this amendment, Applicants

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respectfully request reconsideration and withdrawal of the rejection of claim 25 under 35 U.S.C. §§ 112 and 101.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-7, 10-21, and 24-25 under 35 U.S.C. § 112, first paragraph, alleging that the specification "does not reasonably provide enablement for producing any and all non-human animals exhibiting bone metastasis of any and all tumor cells." Action at page 3. Solely to expedite prosecution and without acquiescing to the rejection, applicants have cancelled claims 6 and 20, and have amended claims 1-5, 7, 10, 13-16, 24, and 25 to recite "rodent" rather than "non-human."

The specification indicates that "[a]nimals which belong to rodents, for example, mouse, rat, hamster, and the like, are preferably used in the present invention." Specification at page 8, second paragraph. In addition to mice, one skilled in the art would be able to use the teachings of the specification to make, e.g., a rat bone metastasis model animal. Nude rats were well known in the art at the time of filing, and were known to be immunodeficient and lack a host versus graft response. See, e.g., Marshall E., et al. (1981) *Aust. J. Exp. Biol. Med. Sci.* 59: 287-96, enclosed herewith. One skilled in the art would therefore have been able to apply the teachings of the specification to rats. For instance, the specification teaches that a "nude mouse which is deficient of T cell function due to lack of thymus...is used as a immunodeficient model for implanting tumor." Specification at page 8, last paragraph, to page 9, first paragraph. One skilled in the art would be able to use a nude rat, which also lacks a thymus and is immunodeficient, in place of the nude mouse without undue experimentation. The specification teaches introduction of the tumor cells

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intravenously, and evaluation of bone metastases by X-ray photography. Each of these procedures was known in the art and used on rats at the time the application was filed. Therefore, the specification enables the use of not only mice, but other rodents such as rats, in the claimed bone metastasis model.

The Examiner alleged that "the specification fails to address the issue of graft versus host disease and immune rejection in non-autologous tumor grafts." Action at page 5. The Examiner concluded that the specification is allegedly "only limited to practice of present invention in immunodeficient animals to support the foreign tumor cells." Action at page 6. Solely to expedite prosecution and without acquiescing to the rejection, applicants have amended claim 1 to recite "wherein the animal is immunodeficient." Claims 2-5 and 7-9 are dependent from claim 1. Claims 24 and 25 are methods involving the rodent bone metastasis model of any of claims 1 to 5, 7, or 9. Claim 10 recites "providing a rodent having reduced immunity..." and claims 11-19 and 21 are dependent from claim 10. Therefore, applicants assert that the rejection is moot because each of the pending claims recites a rodent that is immunodeficient or has reduced immunity.

The Examiner alleged that

> the specification does not provide any guidance for the practice of the present invention in other forms of immunocompromised mice encompassed by the claims or for the level or type of immunodeficiency that will allow any tumor cells to metastasize to the bone for example: genetically immunodeficient mice versus radiation/chemically induced immunodeficient mice.

Action at page 6. Applicants respectfully traverse. As the specification indicates, "[i]mmunodeficient animals may be obtained or produced by way of known means in the art." Specification at page 8, third paragraph. The specification suggests the use of a

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nude mouse, a SCID mouse, a mouse whose NK cells are depleted or inactivated, e.g., by treatment with an anti-asialo-GM1 antibody or an anti-IL-2 receptor antibody, and an x-irradiated mouse. See, e.g., specification at page 8, last paragraph, to page 9, first paragraph. Genetically immunodeficient animals, such as nude rats, nude mice, and SCID mice, were known in the art at the time of filing and could be obtained commercially. The use of chemical means of immunosuppression, such as treatment with anti-asialo-GM1 or anti-IL-2 receptor antibody, was also known in the art at the time of filing. See, e.g., Yano, S. et al. (1996) *Int. J. Cancer* 67: 211-217, cited by the Examiner (hereafter "Yano"). Finally, radiation-induced generation of immunodeficient mice was also known in the art at the time of filing. See, e.g., Takeuchi, M. and Shibata, H. (1997) *J. Vet. Med. Sci.* 59: 413-414, enclosed herewith (hereafter "Takeuchi"). Therefore, applicants assert that genetically-, chemically-, and radiation-induced forms of immunosuppression were known in the art at the time of filing.

The Examiner alleged that the specification discloses using the method of Japanese patent No. 3040451, and indicates that "[a]pplicant is required to amend the disclosure to include the material incorporated by reference." Action at page 7. The specification states that "[a]lthough anti-mouse IL-2 receptor β chain monoclonal Ab, TM-β1 (IgG2b), was kindly supplied by Drs. M Miyasaka and T. Tanaka (Osaka University, Osaka, Japan), it can be produced according to the method described in Japanese Patent No. 3040451 (Tanaka, T. et al., J. Exp. Med. 178: 1103-1107, 1993)." Specification at page 9, second full paragraph. Applicants assert that methods of producing antibodies to known antigens were well known at the time of filing the application, so the specification need not describe such a method. Moreover, many antibodies to IL-2 receptor β chain (also called CD122) are available commercially,

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including TM-β1. See, e.g., pages from the BD Biosciences website and PharMingen Technical Data Sheet for TM-β1, enclosed herewith.

The Examiner alleged that "[t]he specification does not teach what characteristics of a tumor cell will lead it to metastasize to bone." Action at page 7. Applicants respectfully traverse. The specification points out, for example, that in previous studies "it was reported that PTHrP-expression in primary tumors directly correlated with the incidence of bone metastasis in breast cancer patients." Specification at page 11, last paragraph. The specification also notes that "[c]onsistent with the formation of bone metastasis by SBC-5 cells, the levels of PTHrP and calcium in the mouse serum were increased in a time-dependent manner, suggesting that PTHrP produced by human lung cancer may play a crucial role in the formation of bone metastasis and hypercalcemia." Specification at page 2, second full paragraph.

The Examiner alleged that "the specification does not disclose what level of X-rays to use which correlate with inactivating NK cell function." As discussed above, the use of X-ray irradiation to inactivate NK cells was known in the art at the time of filing. See, e.g., Takeuchi.

In view of the foregoing amendments and arguments, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 102

The Examiner rejected claims 1, 3-10, 12, and 19-25 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,643,551 (hereafter "Namikawa"). Specifically, the Examiner alleged that Namikawa discusses

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> a non-human animal, wherein the non-human mammal is a SCID mouse in which tumor cells are introduced by peripheral administration including intravenous, intraperitoneal or subcutaneous injection, and wherein the tumor cells used comprise lung or small cell lung carcinoma or breast and show an increased ability to migrate to bone marrow and cause tumor growth within. [Namikawa] also teaches evaluation of treatments against tumor metastasis using the disclosed model.

Action at page 9 (citations omitted). Applicants respectfully traverse. Namikawa requires the prior introduction of viable human tissue which can thereafter be colonized with human metastatic cells. Specifically, Namikawa discusses "non-human mammals *having a viable, human xenographic organ or tissue* which is capable of being colonized with human metastatic cells." Namikawa at column 2, lines 10-12 (emphasis added). Namikawa further explains that "[t]umor cells are introduced into the chimeric animal after the normal human tissue is implanted." Namikawa at column 2, lines 12-13. Moreover, Namikawa only discusses metastasis of tumor cells from one human xenograph to another. For example, in column 9, lines 46-51, Namikawa states that "[t]he animals were implanted with two pieces of fetal bone from the same donor subcutaneously in distans, 8-10 weeks before injection of the tumor cells. Leukemia cells were injected in only one of the bones so that the movement of the leukemia cells between two bones could be observed later."

In contrast, the claimed invention exhibits metastasis of injected tumor cells in the animal's own bone tissue. See, e.g., Figure 1. Claim 1 recites "[a] rodent bone metastasis model animal exhibiting bone metastasis of tumor cells, in which tumor cells that induce bone metastasis have been introduced by peripheral administration, and wherein the animal is immunodeficient." Claims 3-5, 7, and 9 are dependent from claim 1. Claim 10 recites "[a] method for producing a rodent exhibiting bone metastasis of tumor cells, comprising: (i) providing a rodent having reduced immunity; and (ii)

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introducing tumor cells that induce bone metastasis into the animal by peripheral administration." Claims 19 and 21-23 are dependent from claim 10. Claim 24 recites "[a] method for evaluating efficiencies of treatment against bone metastasis of tumor cells, comprising: (i) applying a treatment to the rodent bone metastasis model animal according to any one of claims 1 to 5, 7, or 9; and (ii) comparing the size and/or extent of bone metastasis, and/or symptoms resulted from bone metastasis, with control animal." Claim 25 recites "[a] method for determining the effect of a test substance on bone metastasis, comprising: (i) administering the test substance to the rodent bone metastasis model according to any of claims 1 to 5, 7, or 9; and (ii) comparing the size and/or extent of bone metastasis, and/or symptoms resulted from bone metastasis, with control animal."

Thus, Namikawa teaches a fundamentally different invention based on an animal that must first be implanted with viable, human xenographic organs or tissues in order to study metastasis of subsequently injected tumor cells. Therefore, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Namikawa.

Rejection Under 35 U.S.C. § 103 (a)

The Examiner rejected claims 2, 11, and 13-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Namikawa in view of Yano and Mundy. For the reasons discussed above, applicants assert that Namikawa teaches an invention that is fundamentally different from the claimed invention. Indeed, the requirement for prior implantation of viable human tissue that is thereafter the host for the human tumor cells teaches away from the instant invention. Furthermore, in the Namikawa model,

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metastasis occurs from one human xenograph to another, rather than to the animal's own bone tissue, as is claimed in claims 2, 11, and 13-18. Claim 2 is dependent from claim 1, and claims 11 and 13-18 are dependent from claim 10. As discussed above, claims 1 and 10, and therefore claims 2, 11, and 13-18, each recite a rodent exhibiting bone metastasis of tumor cells in the animal's own bone tissue.

Yano discusses a mouse metastasis model in which metastasis occurs in the lymph nodes, liver, and kidneys. Out of about 67 mice that were injected with tumor cells, Yano did not obtain any bone metastases. Applicants assert that Yano also teaches away from the invention, and one skilled in the art would not have a reasonable expectation of success that the methods of Yano would produce a bone metastasis in the animal's own bone. Yano therefore fails to remedy the deficiencies of Namikawa.

Mundy also fails to demonstrate that peripheral injection of tumor cells results in bone metastasis, and therefore also does not remedy the deficiencies of Namikawa.

Applicants assert that the primary and secondary references relied upon for the rejection under 35 U.S.C. § 103(a) each teach away from the instant invention, and that the combination of references compounds that deficiency. Thus, there is no motivation to combine these references and no reasonable expectation of success that the combination of references would produce a bone metastasis model animal in which peripherally injected tumor cells metastasize to the animal's own bone. Therefore, the Examiner has failed to establish a prima facie case of obviousness. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Namikawa in view of Yano and Mundy.

Applicants respectfully assert that the present application is in condition for allowance and request that the Examiner issue a timely Notice of Allowance for pending

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claims 1-5, 7, 9-19, and 21-25. If the Examiner does not consider the application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6656 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: July 12, 2002

By: _____
Rebecca B. Scarr
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APPENDIX TO AMENDMENT

Version with Markings to Show Changes Made

IN THE CLAIMS:

Please amend claims 1-5, 7, 9, 10, 13-16, 24 and 25 as follows:

1. (Amended) A [non-human] rodent bone metastasis model animal exhibiting bone metastasis of tumor cells, in which tumor cells [capable of inducing] that induce bone metastasis have been introduced by peripheral administration, and wherein the animal is immunodeficient.

2. (Amended) The [non-human] rodent bone metastasis model animal according to claim 1, wherein the tumor cells are human lung cancer or breast cancer derived cells highly expressing PTHrP.

3. (Amended) The [non-human] rodent bone metastasis model animal according to claim 1, wherein the tumor cells are cells from human lung small cell carcinoma.

4. (Amended) The [non-human] rodent bone metastasis model animal according to claim 1, which exhibits multi-organ metastasis of tumor cells.

5. (Amended) The [non-human] rodent bone metastasis model animal according to claim 4, wherein the multi-organ metastases include metastases to one or more organs selected from [the group consisting of] lung, liver, kidney, and lymph node.

7. (Amended) The [non-human] rodent bone metastasis model animal according to claim [4] 1, wherein the animal is a mouse.

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9. (Amended) The [non-human] rodent bone metastasis model animal according to claim [8] 7, wherein the animal is a SCID mouse.

10. (Amended) A method for producing a [non-human animal] rodent exhibiting bone metastasis of tumor cells, comprising [the steps of]:

(i) providing a [non-human animal] rodent having reduced immunity; and

(ii) introducing tumor cells [capable of inducing] that induce bone metastasis into the animal by peripheral administration.

13. (Amended) The method according to claim 10, wherein the step of providing a [non-human animal] rodent having reduced immunity includes a step of inactivating NK cells in the animal.

14. (Amended) The method according to claim 10, wherein the step of providing a [non-human animal] rodent having reduced immunity includes a step of reducing the number of NK cells in the animal.

15. (Amended) The method according to claim 10, wherein the step of providing a [non-human animal] rodent having reduced immunity includes a step of depleting NK cells in the animal.

16. (Amended) The method according to claim 10, wherein the step of providing a [non-human animal] rodent having reduced immunity includes a step of administering anti-IL-2 receptor antibody to the animal.

24. (Amended) A method for evaluating efficiencies of treatment against bone metastasis of tumor cells, comprising [the step of]:

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(i) applying a treatment to the [non-human animal] rodent bone metastasis model animal according to any one of claims [1 to 9] 1 to 5, 7, or 9; and

(ii) comparing the size and/or extent of bone metastasis, and/or symptoms resulted from bone metastasis, with a control animal.

25. (Amended) [Use of the non-human bone metastasis model animal according to claim to any one of claims 1 to 9 for determining the effect of a test substance on bone metastasis] A method for determining the effect of a test substance on bone metastasis, comprising [the steps of]:

(i) administering the test substance to the [animal] rodent bone metastasis model animal according to any of claims 1 to 5, 7, or 9; and

(ii) comparing the size and/or extent of bone metastasis, and/or symptoms resulted from bone metastasis, with a control animal.

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